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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/043,366	KATSUYAMA, IWAO	
	Examiner	Art Unit	
	Daniel Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *41 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,15-20,23-40 and 43* is/are rejected.

7)☒ Claim(s) *13,14,21 and 22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the Response to Restriction Requirement (Paper No. 5) filed July 9, 2002. Claims 1-40 and 43 are pending in the application.

Election/Restrictions

Claims 41 and 42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 5.

Applicant's traversal of the restriction requirement has been fully considered but is not found to be persuasive. Applicant argues that the restriction requirement is improper because the claims of Group I are related to the claims of Group II in that they recite an experimental animal. The claims of Group II are not, however, drawn to an experimental animal or a method that comprises the use of an experimental animal, as are the claims of Group I. The claims of Group II are drawn to a medicine for treatment or improvement of a corneal epithelial damage. The animal recited in Group II is actually a component of the process by which the medicine of Group II is identified and is therefore not given patentable weight. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) states: "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." Because the medicine obtained by the recited process would not differ from the same medicine obtained

by any other process, the process is immaterial and the claims are simply drawn to a medicine. Because a medicine useful for treatment or improvement of a corneal epithelial damage is different from an experimental animal model or a method comprising said animal model, the inventions are distinct.

Applicant also asserts that there is no search burden because a thorough search of the prior art for any one of the inventions would include the classes and subclasses of the other invention. The argument is not persuasive because, clearly, a thorough search of a medicine capable of treating a condition must encompass all methods of identifying that medicine, and a search of an animal model of a disease state should not be limited only to a search of medicines that can be discovered using the animal model. Therefore the inventions comprise non-overlapping subject matter, which must be searched separately. Thus, restriction between the inventions of Group I and Group II is proper.

The requirement is still deemed proper and is therefore made FINAL.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Drawings

The drawings are objected to for the reasons provided on the attached PTO-948. A proposed drawing correction or corrected drawings are required in reply to the Office action to

avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because it contains legal phraseology (e.g. "the therapeutic effect thereof on said disease"). Correction is required. See MPEP § 608.01(b).

Claim Objections

Claims 9, 13 and 21 are objected to because of the following informalities: In line 2 of claim 9 the plural saccharides should be singular, and in claims 13 and 22 "mammalian" should be mammal. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-4,7-12, 15-20 and 23-26 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to an experimental animal and methods comprising an experimental animal, wherein said experimental animal, as defined in the specification in the second full paragraph of page 13, encompasses a human being. Amending the claims so that they are directed to an experimental *non-human* animal would obviate this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4, 12, 20 and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to

make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention: The invention is directed to an animal model of dry eye and methods of using said animal model.

Breadth of the claims: The claims encompass an animal model wherein "the corneal epithelial damage is dry eye", which is defined in the specification (page12, lines 4-8) as "a group of symptoms which are caused by endogenous diseases such as ocular xerosis, Sjogren's syndrome and Stevens-Johnson syndrome, or exogenous causes such as surgical operation, medicines, trauma, contact lens, and the like".

State of the prior art: Although the prior art teaches several animal models designed to mimic one or more symptoms of dry eye, none claims to be a comprehensive model of the conditions listed above. The closest related art (Gilbard et al. (1984) *Ophthalmology* 91:1205-1212) teaches that, "the morphologic changes that occur in vivo at osmolarities that are observed in [keratoconjunctivitis sicca] are the major corneal changes observed in this disease". However, Fujihara et al. (*J. Ocular Pharm.* (1995) 11:503-508), in a recent publication describing an animal model of dry eye similar to the model of the instant application, teach that "[t]his model is not intended to be a precise representation of the dry eye syndrome, since this disorder has recently become recognized to involve a primary pathological process of the corneal and conjunctival epithelium" (page 503, ABSTRACT).

Amount of direction provided by the inventor: The disclosure describes an animal model, which "shows the symptom of corneal abrasion" (page 18, line 7). The disclosure does not teach that the methods of the instant application produce the pathological processes alluded to by

Fujihara or the group of symptoms caused by the diseases and exogenous causes set forth in the specification.

Relative skill of those in the art: The relative skill in the art is high, however the teachings of the prior art and specification would not provide one of ordinary skill in the art with the means to make or use the animal model of the claimed invention without undue experimentation to produce the symptoms and pathological processes of dry eye.

Quantity of experimentation needed to make or use the invention: Given that dry eye, as defined by applicant, comprises a group of symptoms associated with various syndromes or trauma, and the corneal damage produced by the methods of the instant application is characterized simply as abrasion, significant empirical experimentation would be required to produce the group of symptoms associated with the conditions beyond corneal abrasion. Therefore, the teachings of the specification and prior art would not allow the skilled artisan to make an animal wherein the corneal epithelial damage is dry eye without significant, and undue, experimentation to produce the symptoms and pathological processes that are characteristic of the condition.

Claims 1-4, 7-12, 15-20, 23-28, 31-40 and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a non-human animal model wherein the ocular cornea is covered with a water permeable membrane or tissue, does not reasonably provide enablement for all experimental animal models as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims encompass an animal model and method of using said animal model wherein corneal epithelial damage is induced by the application of an osmotic agent to the ocular cornea. According to the specification, "[a]ny experimental animal may be used for the purpose of the present invention insofar as the eyeball of the animal has a size suitable for use in a pharmacological assay system" (page 8, line 19-21). However, the specification also teaches that, "[w]hen [the] water-absorbing material contacts with the corneal surface, the osmotic pressure in the outside of the epithelium cells is higher than that in the inside of said cells. This leads to loss of the intracellular fluid from the corneal epithelium and produce the corneal epithelial damage" (page 7, lines 15-19). Therefore the teachings of the specification indicate that the method of inducing corneal damage requires that the water-absorbing material create an osmotic gradient across the corneal epithelium. It is known in the art that the cornea of many reptiles is covered with a water impermeable layer (see Underwood, *The Eye* in Biology of the Reptilia, Volume 2 (Gans, C. ed.) Academic Press, London and New York, 1970; see especially the second and third paragraph on page 14), which would prevent damage to the cornea when the water absorbing material is applied according to the teachings of the instant disclosure. Neither the specification nor the prior art teaches a method of making an experimental animal model of dry eye wherein an osmotic agent is applied to the eye of an animal wherein the eye is covered with a water impermeable barrier. The skilled artisan would not predict success in making such a model using the teachings of the specification and prior art, and would have to engage in empirical experimentation to obtain such a model. Therefore practicing the invention commensurate with the full scope of the claims would place an undue burden of experimentation on one of ordinary skill in the relevant art.

In addition, the skilled artisan is not enabled to practice the invention of claims 27, 28, 31-40 and 43 to the extent that they are drawn to a method of making or method of using the nonstatutory human animal model described above in rejection of the product claims under 35 U.S.C. § 101.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in that they are drawn to the experimental animal of claim 27, while claim 27 is drawn to a method of screening or evaluating medicine. It would appear that applicant intends that the claims be directed to the method of claim 27 and, in the interest of compact prosecution, the claims have been examined on the merits with that assumption.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 5-8, 10 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Gilbard et al. (*supra*).

Claims 1, 3, 5-8 and 10 are drawn to an experimental animal having corneal epithelial damage caused by contacting an ocular cornea of said animal with a water-absorbing material. Claim 3 limits the contacting with a water-absorbing material to a whole area of the ocular cornea or a part thereof, or with a pupil area; claim 5 limits the experimental animal of claim 3 to a non-human mammal or a fowl; and claim 6 limits the experimental animal of claim 3 to a rabbit. Claim 7 limits the water-absorbing material of claim 3 to a material including at least one of a polyol, a salt, an amino acid, a peptide and a water-soluble polymer; claim 8 limits the water absorbing material of claim 3 to a material including at least one of a saccharide, an alkali metal salt or an alkali earth metal salt; and claim 10 limits the water soluble material of claim 3 to a material in the physical state of a powder, solution, gel, jelly and tablet.

Gilbard teaches an experimental animal having corneal epithelial damage caused by contacting an ocular cornea with a water-absorbing material (see especially IN VIVO STUDIES, beginning on page 1209 and continuing through page 1211, and Figures 5 and 6 and the captions thereto), said contacting being with the whole area of the ocular cornea, said animal being a rabbit, and said water-absorbing material being a hypertonic salt solution comprising an alkali metal salt and an alkali earth metal salt (Alcon BSS, see **Preparation of solutions** on page 1207 and the formulation of Alcon BSS). The experimental animal, mode of contacting and water-absorbing material taught by Gilbard are the same as those taught in the instant application, therefore the claims are anticipated by Gilbard.

Claim 43 is drawn to a method of making an experimental animal having corneal epithelial damage comprising the step of contacting an ocular cornea of said animal with a water-absorbing material. Gilbard teaches a method of making the animal described above comprising contacting an ocular cornea of said animal with a water-absorbing material (see especially **Experimental procedure**, beginning on page 1207 and continuing through the first full paragraph on page 1208). The method taught by Gilbard is the same as the method taught in the instant application, therefore the limitations of the claim are met by Gilbard.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 27, 29-32, 34 and 38-40 rejected under 35 U.S.C. 103(a) as being unpatentable over Yerxa et al. (1999; U.S. Patent No. 5,900,407) in view of Gilbard (1984; *supra*) and in further view of Fujihara (*supra*).

The claims are drawn to a method of screening or evaluation of a medicine comprising: contacting an ocular cornea of an experimental animal with a water-absorbing material to produce corneal epithelial damage; administering a medicine to the damaged ocular cornea; and evaluating the therapeutic effect thereof on the corneal epithelial damage.

Yerxa teaches a method of evaluating a medicine comprising damaging the corneal epithelium, administering medicine to the damaged area and evaluating the therapeutic effect of said medicine (see especially column 11, EXAMPLE 3). In the method of Yerxa, corneal epithelial damage is produced by surgically closing the lacrimal gland excretory duct; removing the nictitating membrane, nictitans gland and Harderian gland; and waiting 8 weeks for symptoms of dry eye to develop. Yerxa does not teach contacting the cornea with a water-absorbing material to produce corneal epithelial damage.

As described above, Gilbard teaches a method of quickly inducing corneal epithelial damage comprising contacting an ocular cornea of an experimental animal with a water-absorbing material, wherein "the morphologic changes that occur in vivo...are the major corneal changes observed in [dry eye]" (page 1211, column 2, first full sentence). It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Yerxa to include the experimental animal model taught by Gilbard according to the method of the instant application. Motivation to combine these teachings comes from the relatively rapid development of symptoms of dry eye in the experimental animal model of

Gilbard, approximately 6 hours (see especially Figure 4 and the caption thereto), as opposed to the model used by Yerxa, which required 8 weeks for symptoms to develop. Further motivation comes from the teachings of Fujihara, who teaches that animal models for dry eye, including rabbits with lacrimal glands removed, "are not suitable for use in initial screening of therapeutic agents because of delayed or absence of clinical signs, variability and occasional spontaneous recovery" (page 507, first paragraph). The skilled artisan would therefore be motivated to use the animal model taught by Gilbard, which provides an experimental animal that rapidly develops clear clinical characteristics of dry eye, to overcome the art recognized deficiencies of other animal models of dry eye. One would have a reasonable expectation of success in combining these teachings because the animal model of Gilbard can simply be substituted in method of Yerxa without modification of either teaching.

Claim 29 limits the experimental animal of the claimed method to a non-human mammal or a fowl; claim 30 limits the experimental animal to a rabbit; claim 31 limits the water-absorbing material to a polyol, a salt, an amino acid, a peptide or a water-soluble polymer; claim 32 limits the water-absorbing material to a saccharide, an alkali metal salt or an alkali earth metal salt; claim 34 limits the physical state of the water-absorbing material to a powder, a solution, a gel, a jelly or a tablet; claim 38 adds the method steps of staining the damaged area of the ocular corneal epithelium either (a) after administration of the medicine, or (b) before and after administration of the medicine and evaluating the therapeutic effect of the medicine based on change in the stained area of the ocular corneal epithelium; and claims 39 and 40 limit the medicine to an eye drop.

All of the above claim limitations are taught by either Yerxa or Gilbard. Both Yerxa and Gilbard teach an animal model that is a rabbit. As described above, Gilbard teaches a water-absorbing material comprising an alkali metal salt and an alkali earth metal salt in solution. The method of Yerxa also comprises the method steps of staining of goblet cells with alcian blue and periodic acid-Schiff's reagent, and a medicine that is a solution of UTP that is administered as a drop. Therefore, each embodiment of the claimed invention set forth in the dependent claims would have been obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

Claims 14 and 22 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
September 26, 2002

Anne-Marie Falk
ANNE-MARIE BAKER
PATENT EXAMINER